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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BADGER, Alison, Mary [US/US]; 56 Parkridge Drive, Bryn Mawr, PA 19010 (US).

(74) Agents: DUSTMAN, Wayne, J. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: METHOD OF INHIBITING THE PRODUCTION OF HUMAN IMMUNODEFICIENCY VIRUSES WITH SUBSTITUTED AZASPIRANES

(57) Abstract

Invented is a method of inhibiting the production of infectious human immunodeficiency viruses (HIV) in HIV seropositive humans which comprises administering to such human an effective amount of a substituted azaspirane.

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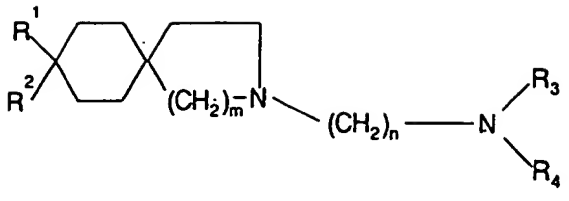
METHOD OF INHIBITING THE PRODUCTION OF HUMAN IMMUNODEFICIENCY VIRUSES WITH SUBSTITUTED AZASPIRANES

This invention relates to a method of inhibiting the production of infectious human immunodeficiency viruses (HIV) in HIV seropositive humans which comprises administering to such human an effective amount of a substituted azaspirane.

Background of the Invention

Numerous agents are presently available that inhibit the replication of human immunodeficiency viruses in T cells and monocytes (Yarchoan et al., Lancet (1986); 1:575-580 and Broder et al., Lancet (1985); 3:627-630). These compounds are limited in their usefulness due to significant toxicities and viral resistance associated with their long-term use Volberding, et al., N. Engl J. Med 1990; 322:941-949. Additionally, certain selected immunosuppressive/immunomodulatory agents have demonstrated an ability to suppress viral replication. Specifically, immunomodulating CD8 lymphocytes have been shown to suppress replication of HIV in peripheral blood mononuclear cells (Walker et al. Science, 234:1563-6 (1986)) and activated CD8+ T cells have been shown to inhibit the replication of HIV in cultures of CD4+ cells from asymptomatic HIV seropositive individuals (Brinchmann et al. CD8+ T cells J. Immunol. 144 2961-2966 (1990)). Further, the immunosuppressive compound cyclosporin A (CsA) has demonstrated a protective effect in several animal models of viral infection. Particularly, chronic treatment with CsA before and after infection with LP-BM5 murine leukemia virus has proven effective against the development of immunodeficiency disease (Cerny, A. et al. Eur. J. Immunol. 21:1747-50 (1991)). Evidence that treatment of AIDS and HIV-seropositive non-AIDS patients with CsA increases T4 cells and inhibits lymphadenopathy has also been reported. (Andrieu et al. Clin. Immunol. and Immumopathol. 46:181-198 (1988)). However, none of the above references suggest that immunosuppressive/immunomodulatory agents in general will have utility in inhibiting the production of infectious HIV in HIV seropositive humans. Further, none of the above references teaches or suggest a means for predicting whether a particular immunosuppressive/immunomodulatory agent will have utility in inhibiting the production of infectious HIV in HIV seropositive humans.

Badger, et al., U.S. Patent No. 4,963,557 (Badger I) discloses compounds of the formula



(I)

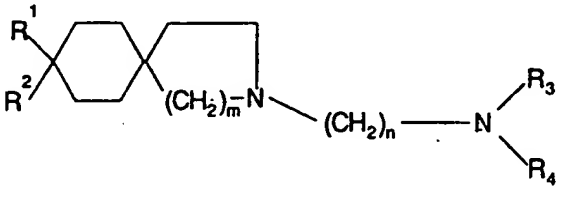
wherein: n is 3-7; m is 1 or 2; R^1 and R^2 are the same or different and are selected from hydrogen or straight or branched chain alkyl, provided that the total number of carbon atoms contained by R^1 and R^2 when taken together is 5-10; or R^1 and R^2 together form a cyclic alkyl group having 3-7 carbon atoms; R^3 and R^4 are the same or different and are selected from hydrogen or straight chain alkyl having 1-3 carbon atoms; or R^3 and R^4 are joined together with the nitrogen atom to form a heterocyclic group having 5-8 atoms; or a pharmaceutically acceptable salt or hydrate or solvate thereof.

Badger I discloses compounds of Formula I as a class of novel compounds which induce an immunomodulatory effect which is characterized by the stimulation of suppressor cell activity.

Badger I does not disclose the compounds of Formula I as agents for inhibiting the production of infectious HIV in HIV seropositive humans.

Summary of the Invention

This invention relates to a method of inhibiting the production of infectious HIV in HIV seropositive humans which comprises administering to such human an effective amount of a compound of the formula



(I)

wherein:

n is 3-7;

m is 1 or 2;

R^1 and R^2 are the same or different and are selected from hydrogen or straight or branched chain alkyl, provided that the total number of carbon atoms contained by R^1 and R^2 when taken together is 5-10; or R^1 and R^2 together form a cyclic alkyl group having 3-7 carbon atoms;

R^3 and R^4 are the same or different and are selected from hydrogen or straight chain alkyl having 1-3 carbon atoms; or R^3 and R^4 are joined together with the nitrogen atom to form a heterocyclic group having 5-8 atoms;

or a pharmaceutically acceptable salt or hydrate or solvate thereof.

Detailed Description of the Invention

The preparation of all compounds of Formula (I) and pharmaceutically acceptable salts, hydrates and solvates and formulations thereof is disclosed in U.S. Patent No. 4,963,557, the entire disclosure of which is hereby incorporated by reference.

A preferred compound used in the novel method is the dihydrochloride salt of a compound of Formula (I) where R^1 and R^2 are propyl, R^3 and R^4 are methyl, m is 1 and n is 3 which is N,N-dimethyl-8,8-dipropyl-2-azaspiro[4.5]decane-2-propanamine dihydrochloride.

A particularly preferred compound used in the novel method is the dihydrochloride salt of a compound of Formula (I) where R^1 and R^2 are propyl, R^3 and R^4 are ethyl, m is 1 and n is 3 which is N,N-diethyl-8,8-dipropyl-2-azaspiro[4.5]decane-2-propanamine dihydrochloride.

A particularly preferred compound used in the novel method is the dihydrochloride salt of a compound of Formula (I) where R^1 and R^2 are propyl, R^3 and R^4 are joined together with the nitrogen to form a piperidine ring, m is 1 and n is 3 which is 8,8-dipropyl-2-azaspiro[4.5]decane-2-piperidinopropyl dihydrochloride.

This invention discloses compounds of Formula (I) and pharmaceutically acceptable salts or hydrates or solvates thereof as being useful for inhibiting the production of infectious HIV in HIV seropositive humans.

The compounds of Formula I are tested for their ability to inhibit the production of infectious HIV in the assay described in Sperber, et al., AIDS Research and Human Retroviruses, 9 No.1, 91-98.

This invention relates to a method of inhibiting the production of infectious HIV which comprises administering to an HIV seropositive human an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or hydrate or solvate thereof. A compound of Formula (I) or a pharmaceutically acceptable salt or hydrate or solvate thereof can be administered to such human in a conventional dosage form prepared by combining a compound of Formula (I) or a pharmaceutically acceptable salt or hydrate or solvate thereof, with a conventional pharmaceutically acceptable carrier or diluent according to known techniques, such as those described in Badger (I), U.S. Patent No. 4,963,557.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. A compound of Formula (I) or a pharmaceutically acceptable salt or hydrate or solvate thereof is administered to an HIV seropositive human in an amount sufficient to inhibit the production of infectious HIV

The route of administration of the Formula (I) ("active ingredient") compound is not critical but is usually oral or parenteral, preferably oral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intranasal, intrarectal, transdermal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 0.01 mg/kg to about 10 mg/kg of total body weight, most preferably from about 0.1 mg/kg to about 1 mg/kg. Preferably, each parenteral dosage unit will contain the active ingredient in an amount of from about 0.1 mg to about 100 mg.

The compounds of Formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavoring or coloring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

The daily oral dosage regimen will preferably be from about 0.01 mg/kg to about 10 mg/kg of total body weight. Preferably each oral dosage unit will contain the active ingredient in an amount of from about 0.1 mg to about 100 mg.

While it is possible for an active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate or solvate thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt or hydrate or solvate thereof given per day and duration of therapy, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The method of this invention of inhibiting the production of infectious HIV in HIV seropositive humans comprises administering to a subject in need of such inhibition an effective infectious HIV inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in the inhibition of infectious HIV in HIV seropositive humans.

The invention also provides for a pharmaceutical composition for use in the inhibition of the production of infectious HIV in HIV seropositive humans which comprises a compound of Formula I and a pharmaceutically acceptable carrier.

The invention also provides for a process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier or diluent and a compound of Formula I which comprises bringing the compound of Formula I into association with the pharmaceutically acceptable carrier or diluent.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the compounds of the present invention can be co-administered with further active ingredients, such as compounds known to prevent or delay the occurrence of AIDS in HIV seropositive humans such as retrovir (the brand name for zidovudine, formerly called azidothymidine (AZT)).

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

EXAMPLE 1 - CAPSULE COMPOSITION

An oral dosage form for administering Formula (I) compounds is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

Table I

INGREDIENTS	AMOUNTS
N,N-diethyl-8,8-dipropyl-2-azaspiro[4,5]decane-2-propanamine dihydrochloride	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

EXAMPLE 2 - INJECTABLE PARENTERAL COMPOSITION

An injectable form for administering Formula (I) compounds is produced by stirring 1.5% by weight of N,N-diethyl-8,8-dipropyl-2-azaspiro[4,5]decane-2-propanamine dihydrochloride in 10% by volume propylene glycol in water.

Example 3 - Tablet Composition

The sucrose, calcium sulfate dihydrate and Formula (I) compound shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

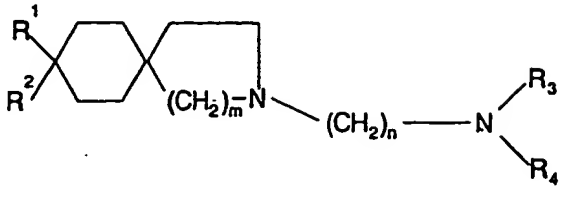
Table II

Ingredients	Amounts
N,N-diethyl-8,8-dipropyl-2-azaspiro[4,5]decane-2-propanamine dihydrochloride	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

While the above descriptions and examples fully describe the invention and the preferred embodiments thereof, it is understood that the invention is not limited to the particular disclosed embodiments coming within the scope of the following claims.

What is claimed is:

1. Use of a compound of the formula



(I)

wherein:

n is 3-7;

m is 1 or 2;

R^1 and R^2 are the same or different and are selected from hydrogen or straight or branched chain alkyl, provided that the total number of carbon atoms contained by R^1 and R^2 when taken together is 5-10; or R^1 and R^2 together form a cyclic alkyl group having 3-7 carbon atoms;

R^3 and R^4 are the same or different and are selected from hydrogen or straight chain alkyl having 1-3 carbon atoms; or R^3 and R^4 are joined together with the nitrogen to form a heterocyclic group having 5-8 atoms;
or a pharmaceutically acceptable salt or hydrate or solvate thereof; in the manufacture of a medicament for inhibiting the production of infectious human immunodeficiency viruses (HIV) in HIV seropositive humans.

2. The use according to claim 1 wherein the compound is N,N-diethyl-8,8-dipropyl-2-azaspiro[4.5]decane-2-propanamine;
or a pharmaceutically acceptable salt, hydrate or solvate thereof.

3. The use according to claim 1 wherein the compound is administered orally.

4. The use according to claim 3 wherein from about 0.01 mg/kg to about 10 mg/kg of compound is administered per day.

5. The use according to claim 1 wherein the compound is administered parenterally.

6. The use according to claim 5 wherein from about 0.01 mg/kg to about 10 mg/kg of compound is administered per day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08275

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 31/40, 31/44, 31/55
US CL :514/409, 212, 278
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/409, 212, 278

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN(REGISTRY(STRUCTURES) & CHEMICAL ABSTRACTS)
search terms: AIDS, HIV

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,963,557 (BADGER ET AL) 16 OCTOBER 1990, see claim 1.	1-6
X	Chemical Abstracts, Volume 117, No. 23, issued 07 December 1992, Badger et al, "Azaspirane Derivatives as Cytokine Inhibitors", see page 83, column 2, abstract no. 226312z, PCT Int. Appl. WO 92/14,462.	1-6
X, P	Chemical Abstracts, Volume 119, No. 17, issued 25 October 1993, Badger, "Preventing or Delaying Occurrence of Acquired Immunodeficiency Syndrome with Azaspiranes", see page 90, column 1, abstract no. 174173z, PCT Int. Appl. WO 93/14,760.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
WILLIAM JARVIS
Telephone No. (703) 308-1235

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